protein crosslinks (Figure 1B, red dashpot) between microtubules. Upon mechanical perturbation, spindle microtubules could relax and reorganize as microtubule crosslinking proteins detach and reattach, or as microtubules simply shrink and regrow, for example. The latter is especially appealing since both the microtubule lifetime and measured mechanical relaxation times are of tens of seconds. As for spindle elasticity, it depends on spindle pole integrity and likely stems from the rigidity of microtubules (Figure 1B, springs): the authors link the rigidity of non-kMTs (green and stiffer spring in series) to short-term elasticity, and that of kMTs (purple and more compliant spring in parallel) to long-term elasticity. Repeating this experiment in spindles assembled without kinetochores and kMTs [16] would allow us to determine whether both microtubule populations do indeed behave as distinct mechanical entities.

The data provided by Shimamoto *et al*. [7] suggest that the spindle can be a mechanically versatile machine by exploiting different functional timescales and axes. Along its long axis the spindle is liquid-like, while along its short axis it can be more liquid- or solid-like at different timescales. Over short timescales (Figure 1B, left), the dynamic microtubule crosslinks do not have time to relieve strain and the stiffest spring, non-KMT rigidity, dominates: non-kMTs, with their short lifetimes, help the spindle robustly keep its integrity in the face of rapid yanks. Over intermediate timescales (Figure 1B, center), these dynamic crosslinks reorganize themselves locally and dominate the response until the system is equilibrated: if the spindle is deformed at such velocities, for example when a chromosome squeezes through, it can accommodate big deformations locally while minimizing an elastic response and maintaining global integrity. Over long timescales (Figure 1B, right), the same dynamic crosslinks reach a new equilibrium, and the most compliant spring, kMT rigidity, dominates the response: kMTs, with their longer lifetimes, give the spindle a long-term mechanical memory of its architecture.

The force the spindle exerts back on its components can thus be very different depending on how fast these move, in which direction they go and where they are in the spindle [17]. Thus not only do nm-scale activities lead to μm-scale material properties, but these material properties may inform — and help coordinate – nm-scale dynamics.

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Department of Systems Biology, Harvard Medical School, Boston, MA 02115, USA.
E-mail: Sophie_Dumont@hms.harvard.edu

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Tissue Polarity: PCP Inheritance Ensured by Selective Mitotic Endocytosis

Recent findings report the selective internalization of core planar cell polarity components during mitosis followed by cell-non-autonomous polarized recycling. This novel mechanistic model explains how tissue polarity is inherited in daughter cells of proliferative tissue.

Nabila Founounou and Roland Le Borgne

Planar cell polarity (PCP) is an evolutionarily conserved mechanism enabling epithelial cells to individually polarize perpendicular to their apicobasal axis. Establishment and maintenance of PCP have been extensively studied in the developing *Drosophila* epidermis [1–5]. Highly regenerative tissues, such as mammalian skin, also exhibit the features of PCP [6,7]. A challenging task for such proliferative tissue is to maintain and accurately propagate PCP information while cells keep dividing at high frequency. A recent study [8], published in *Nature Cell Biology* by the team of Elaine Fuchs, addresses this issue in mouse basal epithelial cells — progenitors that generate hair follicles and outer stratified skin layers. In this study, which combines cutting-edge mouse genetics and state-of-the-art cell biology approaches, Devenport and

colleagues [8] observed that mitotic endocytosis of core PCP components provides a mechanism through which regenerative tissues can maintain PCP at long range.

First identified in *Drosophila* epithelia, a common feature of PCP is the asymmetric distribution of functionally conserved core PCP transmembrane components, including the serpentine receptor Frizzled (Fz/Fzd), the seven-pass transmembrane atypical cadherin Flamingo (Fmi, also known as Starry night) or Celsr (Cadherin, EGF-like, LAG-like, seven pass receptor), and Van Gogh (Vang/Vangl, also known as Strabismus) [1–5,9–13]. While Fz and Vang accumulate at opposite cell edges, Fmi/Celsr1 distributes at both edges. These transmembrane proteins communicate between cells to enable the recruitment of Fzd at one side and Vangl at the opposite side (Figure 1A, inset). Establishment and maintenance of this asymmetry relies on a self-organizing process dependent on feedback loops. In *Drosophila*, Fmi is continuously internalized in the absence of Vang and Fz. Vang and Fz were recently shown to stabilize Fmi via the formation of intrinsically stable asymmetric complexes at the plasma membrane [14]. In a second step, PCP cytoplasmic components, including Dishevelled/Diego and Prickle, which are found at the anterior and posterior cell edges, respectively, locally induce the clustering of the asymmetric complexes (Figure 1A). In contrast to each cell of the *Drosophila* epidermis producing a single trichome (small hair), mouse hair follicles are composed of hundreds of proliferative cells. These cells are oriented as a unit and the orientation is coordinated with that of the neighboring follicles, which are separated from one another by intervening basal epidermal cells and underlying dermis. Previous work from Devenport *et al.* [6] revealed that, despite its high proliferative nature, this tissue exhibits the hallmarks of PCP.

Using mosaic transgenic mouse embryos, the authors further extend this notion by now reporting that, as in the *Drosophila* epidermis, Celrs1 and Vangl2 are asymmetrically distributed in basal interphasic epidermal stem cells of mouse skin. Vangl2 localizes at the anterior edge, while Celsr1 is found at both edges (Figure 1A) [8]. During mitosis, components of intercellular junctions, including E-cadherin, remain evenly distributed at the plasma membrane, where they likely contribute to the preservation of the apicobasal polarity during mitosis. In striking contrast, during prophase Celsr1, Vangl2 and Fzd6 undergo selective and dramatic relocalization into intracellular compartments that are partitioned equally between the two daughter cells (Figure 1). When cultured keratinocytes enter prophase, Celsr1 is relocated from the plasma membrane towards early endosomes and recycling endosomes [8]. As proposed earlier [15], this change in subcellular location could result from increased internalization or reduced recycling back to plasma membrane or both. Total internal reflection fluorescence microscopy on cultured keratinocytes reveals that clathrin-mediated endocytosis of Celsr1 is dramatically increased at mitosis, although a block in Celsr1 recycling could partially contribute to its redistribution as well [8].

What triggers the burst of selective mitotic internalization of PCP complexes is currently unknown. The planar-polarized remodeling of cell junctions during tissue extension, i.e. in the absence of cell division, is controlled by polarized clathrin-mediated endocytosis. Initiation of E-cadherin internalization is mediated by its lateral clustering through the activity of myosin II and Diaphanous [16]. In contrast, lateral clustering of asymmetric PCP complex decreases their internalization rate and results in their stabilization at the plasma membrane in interphase [14]. Thus, upon entry into mitosis, there is an apparent switch in the selection of clathrin-dependent cargo. Studies of the effects of point mutations in the cytosolic tail of Celsr1 suggest that phosphorylation of Celsr1 itself cannot account for its mitotic internalization [8]. An alternative possibility could be a mitosis-specific phosphorylation of components of the endocytic machinery and/or components regulating lateral clustering of cargoes. Additional studies are needed to decipher the molecular switch that operates to regulate internalization at mitosis.

Epistatic analyses in cultured keratinocytes revealed that Celsr1 acts upstream to recruit Vangl2 and Fzd6 in endosomes during mitosis. This leads to the notion that, in dividing basal cells, Celsr1 drives the internalization of Vangl2 and Fzd6 into endosomes to ensure their even partitioning between daughter cells (Figure 1B,C). While Vangl2 and Fzd6 colocalize with

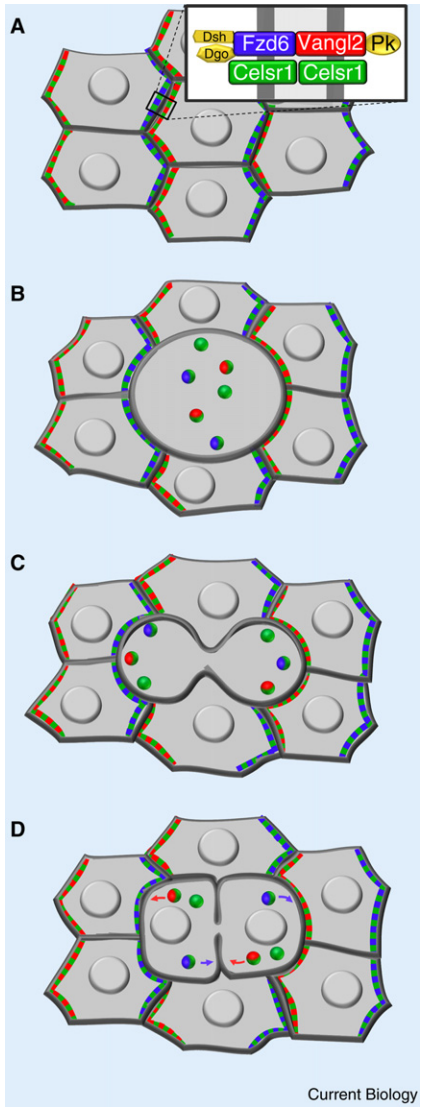

Figure 1. Schematic representation of the mitotic inheritance of core PCP components in mouse basal cells.

(A) In mouse skin epithelium, Celsr1–Fzd6 and Celsr1–Vangl form asymmetric complexes localized at the anterior and posterior edges, respectively. By analogy to *Drosophila*, these components are proposed to interact in *trans*, with their local clustering being mediated by cytosolic Dishevelled, Diego and Prickle (inset). (B,C) During mitosis, Celsr1–Vangl2 and Celsr1–Fzd6 complexes are (B) selectively endocytosed into distinct vesicular endosomes that (C) partition equally between daughter cells at cytokinesis. At this stage, PCP complexes containing endosomes are distributed along the antero-posterior axis. (D) Following cytokinesis, PCP-containing endosomes are predicted to fuse with their cognate antero-posterior plasma membrane to re-establish PCP. Anterior is left in all panels.

Celsr1-positive vesicular compartments, Fzd6 and Vangl2 are found on distinct vesicular compartments *in vivo*, indicating that antero-posterior core PCP asymmetry is preserved during mitosis. How is this endosomal asymmetry maintained? Devenport *et al.* [8] report that, in cultured keratinocytes, mitotically internalized Celsr1 colocalizes with various endocytic markers, including Rab5- and EEA1-positive early endosomes, Rab11-positive recycling endosomes, as well as caveolin [8]. This observation raises the possibility that anterior and posterior cognate PCP complexes could follow distinct endocytic routes to be targeted to distinct classes of endosomes, thereby preventing the different PCP complexes from mixing in mitosis. During cytokinesis, Celsr1-positive compartments are distributed in a polarized manner at the anterior and posterior poles of daughter cells (Figure 1C). Strikingly, endosomal vesicles are shown to interpret antero-posterior cues independently of mitotic spindle orientation. Stunning mosaic experiments revealed that, at this stage, polarisation of the Celsr1-positive endosomes is dictated in a cell-non-autonomous manner by the interphasic neighboring PCP-polarized cells [8]. Whether and how endosomes containing the anterior or posterior PCP complex selectively recognize and fuse with the respective cognate anterior or posterior cortex remains unknown. It will also be interesting to understand how polarized endosomal recycling drives PCP re-establishment at the boundaries of the two daughter cells (Figure 1D). In addition, future studies will assist our understanding of how PCP complexes from neighboring interphasic cells are maintained at the boundaries of mitotic cells.

What are the underlying molecular mechanisms and the biological relevance of selective mitotic internalization? Using a series of domain swapping and point mutation experiments, Devenport *et al.* [8] reveal that a single juxtamembrane di-leucine signal present in the cytoplasmic domain of Celsr1 is necessary to promote its mitotic internalization. Importantly, in clones of cells expressing the endocytic-defective version of Celsr1, hair follicles are no longer aligned along the antero-posterior axis. Mutant cells align one relative to the other, a misorientation that is transmitted in a dominant cell-non-autonomous manner to adjacent wild-type cells [8]. These observations first strongly argue that mitotic internalization of PCP components is physiologically important and second lead to the proposal that mitotic uptake occurs to prevent PCP signaling from the rounded cell, therefore avoiding disruption of PCP by aberrant directional information. Is this mechanism evolutionarily conserved? Perhaps not, given that mitotic internalization of PCP components has not been reported in *Drosophila* [17,18] and mitotic internalization motif of Celsr1 is not conserved in dipters [8]. How then is PCP transmitted in daughter cells in the fly? Clearly, further investigation of mitotic endocytosis of PCP components in model systems will provide new and exciting insights into how polarized trafficking allows inheritance of PCP in tissues.

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CNRS, UMR 6061, Institut Génétique et Développement de Rennes, Université Rennes 1, UEB, IFR 140, F-35043 Rennes, France.
E-mail: roland.leborgne@univ-rennes1.fr

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Protein Degradation: BAGging Up the Trash

Cells efficiently uncover and degrade proteins that are misfolded. However, we know very little about what cells do to protect themselves from mislocalized proteins. A new study reveals a novel quality control pathway that recognizes and degrades secretory pathway proteins that have failed to target to the endoplasmic reticulum.

Tslil Ast and Maya Schuldiner*

Have you ever had the dubious pleasure of finding groceries that you've forgotten to place in the refrigerator? Holding your breath and looking away, the only thing left to do is to promptly throw everything out. In